Acute Decompensated Heart Failure: The Cardio Renal Interaction.

Uri Elkayam, MD
Professor of Medicine
University of Southern California School of Medicine
Los Angeles, California
elkayam@usc.edu
Many Patients Have Little or No Weight Loss During Hospitalization


ADHERE Registry
The management of the hospitalized patient with heart failure

The goal of therapy is the relief of congestion and achieving euvolemia and hemodynamic and symptomatic improvement.

A position statement from the Heart Failure Association of the ESC
European Journal of Heart Failure (2019) 21, 137–155
Targets for Decongestion

- Rates of rehospitalization and death are consistently lower in patients rendered free of clinical congestion by the time of discharge.
- The goal is resolution of edema, orthopnea, and jugular venous distention (<8 cm) *
- Decrease in BNP > 30%.

* inability to lower high RA pressure to a normal JVP a poor prognostic indicator.

A position statement from the Heart Failure Association of the ESC
European Journal of Heart Failure (2019) 21, 137–155
ADHF is a malignant disease

Get With The Guidelines Registry
Medicare Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24374</td>
</tr>
<tr>
<td>Death at 30 days</td>
<td>2903 (12%)</td>
</tr>
<tr>
<td>Rehospitalization or death at 30 days</td>
<td>6988 (29%)</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>9872 (40%)</td>
</tr>
<tr>
<td>Rehospitalization or death at 1 year</td>
<td>17918 (74%)</td>
</tr>
</tbody>
</table>

Circulation HF 2019
Optimize volume status

• Diuretics / Ultrafiltration.
• Vasodilators.
• Inodilators.
How should we use diuretics in patients with AHF?
Delayed absorption of oral furosemide and shift in natriuretic response

Patients with volume overload
Should be treated with IV loop diuretics (Guidelines)

60-70% decrease in natriuretic response

Diuretic resistance

• Diuretic resistance is a failure to increase fluid and sodium (Na+) output sufficiently to relieve volume overload and congestion despite a full dose of a loop diuretic.

• A poor diuretic response predicts subsequent death, readmission, or renal complications from CHF.
Recommendations for diuretic Tx
ESC 2021, ACC/AHA/HFSA 2022

• Daily single bolus administrations are discouraged because of post-dosing sodium retention.
• Furosemide (bumetanide) can be given IV as 2-3 daily.
• 1-2 times the daily oral dose taken prior to hospitalization given IV.
• Boluses or as a continuous infusion.
• With continuous infusion, a loading dose to achieve steady state earlier.
Post – diuretic sodium retention

- A phenomenon that occurs once the loop diuretic concentrations drop below threshold in the renal tubules.
- Sodium reabsorption is enhanced in the distal tubules and collecting ducts and may completely counteract the effects of the loop diuretic.
Recommendations for diuretic Tx
ESC 2021, ACC/AHA/HFSA 2022

- Daily single bolus administrations are discouraged because of post-dosing sodium retention.
- Furosemide (bumetanide) can be given IV as 2-3 daily.
- 1-2 times the daily oral dose taken prior to hospitalization given IV.
- Boluses or as a continuous infusion.
- With continuous infusion, a loading dose to achieve steady state earlier.
Recommendations for diuretic Tx
ESC 2021, ACC/AHA/HFSA 2022

• Daily single bolus administrations are discouraged because of post-dosing sodium retention.
• Furosemide (bumetanide) can be given IV as 2-3 daily.
• 1-2 times the daily oral dose taken prior to hospitalization given IV.
• Boluses or as a continuous infusion.
• With continuous infusion, a loading dose to achieve steady state earlier.
# Low vs. High Dose

## Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low dose</th>
<th>High dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=151</td>
<td>N=157</td>
<td></td>
</tr>
<tr>
<td>AUC for dyspnea</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight loss (Lb.)</td>
<td>-6.1±9.5</td>
<td>-8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Chang in NTproBNP (pg/ml)</td>
<td>-1194±4094</td>
<td>-1882±4105</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Low dose = Total daily oral dose. (80mg=80mg IV)
High Dose = 2.5 X total daily oral dose (80mg=200mg IV)
CARESS – HF

Goal: 3–5 L/day

CARESS trial
Aggressive diuresis vs Ultrafiltration

Diuretic Dosing Table

<table>
<thead>
<tr>
<th>Step</th>
<th>Loop (l/day)</th>
<th>Thiazide</th>
<th>Loop (l/day)</th>
<th>Thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≤ 80</td>
<td>= 40 mg iv bolus + 3 mg/hr</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>81 - 160</td>
<td>= 80 mg iv bolus + 10 mg/hr</td>
<td>5 mg metolazone qd</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>161 - 240</td>
<td>= 80 mg iv bolus + 20 mg/hr</td>
<td>5 mg metolazone bid</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>&gt; 240</td>
<td>= 80 mg iv bolus + 30 mg/hr</td>
<td>5 mg metolazone bid</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. The urine output–guided stepwise pharmacologic care algorithm for diuretic adjustment. *Presence of persisting volume overload. †Dopamine or dobutamine at 2 μg kg⁻¹ min⁻¹ if systolic blood pressure (SBP) <110 mm Hg and left ventricular ejection fraction (LVEF) <40% or RV systolic dysfunction; or nitroglycerin of nesiritide if SBP >120 mm Hg (any LVEF) and severe symptoms. ‡Hemodynamics-guided intravenous therapy, left ventricular assist device, dialysis, or ultrafiltration crossover.

Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group. The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.
## Bolus vs. Continuous

Results over 72 hours

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bolus N=156</th>
<th>Continuous N=152</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea</td>
<td>4456±1448</td>
<td>4699±1573</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight loss (Lb.)</td>
<td>-6.8±7.8</td>
<td>-8.1±10.3 (19%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Net fluid loss (ml)</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
</tr>
<tr>
<td>NTproBNP (pg/ml)</td>
<td>-1316±4364</td>
<td>-1773±3828</td>
<td>0.44</td>
</tr>
</tbody>
</table>

- No bolus prior to infusion
- Higher dose in the bolus arm 200 mg/d vs 160 mg/d (p=0.06)
- Bolus required more frequent dose adjustment
Figure 1. Furosemide plasma concentration (top) and urinary furosemide excretion rate (bottom) for a representative study patient (Patient 1) after 500 mg of furosemide as a bolus injection or continuous infusion (50 mg/h during 8 h preceded by a loading dose of 100 mg).
Figure 13: Diuretic therapy (furosemide) in acute heart failure. i.v. = intravenous. The maximal daily dose for i.v. loop diuretics is generally considered furosemide 400—600 mg though up to 1000 mg may be considered in patients with severely impaired kidney function. Combination therapy is the addition to the loop diuretic of a diuretic with a different site of action, e.g., thiazides or metolazone or acetazolamide. Modified from 145.
Diuretic dose – response relationship in cardiorenal syndrome

Figure 6. | Diuretic dose-response relationship in cardiorenal syndrome. (A) The loop diuretic dose-response curve is shown for healthy normal controls (blue line) and patients with ADHF (red line). Sodium (Na⁺) excretion is plotted against the plasma diuretic concentration on a logarithmic scale. Compared with normal, patients with ADHF have rightward (R) shift and downward (D) shift in the dose-response curve. Patients with ADHF require a significantly higher loop diuretic dose and have a diminished ceiling response. Adapted from ref. 8, with permission. (B) Patients with ADHF and diuretic resistance were given ascending doses of iv furosemide (blue bars). FENa increased with ascending furosemide doses up to approximately 500 mg. The incremental improvements in natriuresis occurred with doses commonly considered to be above the diuretic “ceiling” and illustrate the rightward shift of the dose-response curve in ADHF. Adapted from ref. 30, with permission. *IV furosemide equivalents where 1 mg iv bumetanide=40 mg iv furosemide.

Classic and Novel Mechanisms of Diuretic Resistance in Cardiorenal Syndrome
Cox ZL et al KIDNEY 360 3: 954–967, 2022
Bolus Vs Continuous infusion

• Importantly, continuous infusion has not shown meaningful superiority over bolus diuretic administration.

• However, the use of a significantly higher total daily loop diuretic dose administered as an infusion, could be the preferred strategy for patients with a highly sodium avid substrate.

• Thus, patients with significant diuretic resistance may be optimally treated with both higher diuretic doses and frequent dosing/continuous infusion.
COMPARATIVE EFFECT ON URINE OUTPUT
Ng T, Elkayam U et al J CV Pharm Therapy 2012

### Bar Chart

<table>
<thead>
<tr>
<th>Regimen</th>
<th>UO Baseline (mL/h)</th>
<th>UO on Tx (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIF</td>
<td>114</td>
<td>168</td>
</tr>
<tr>
<td>F+M</td>
<td>96</td>
<td>208</td>
</tr>
<tr>
<td>CIB</td>
<td>89</td>
<td>177</td>
</tr>
</tbody>
</table>

Mean difference b/w baseline and refractory regimen:
- CIF: -48±103*
- F+M: -109±171*†
- CIB: -90±90*†

* p<0.0001 vs baseline
† p<0.0087 between groups

- CIF: Continuous infusion furosemide
- F+M: Furosemide + metolazone
- CIB: Continuous infusion Bumetanide
The Breaking phenomenon

Angiotensin II
Aldosterone
COMPARATIVE EFFECT ON URINE OUTPUT
Ng T, Elkayam U et al  J CV Pharm Therapy  2012

Mean difference b/w baseline and refractory regimen
-48±103\(^*\)  -109±171\(\uparrow\)  -90±90\(\uparrow\)

\(\*p<0.0001\) vs baseline
\(\uparrow p<0.0087\) between groups

Continuous infusion
furosemide

Furosemide +
metolazone

Continuous infusion
Bumetanide
## COMPARATIVE EFFECT ON URINE OUTPUT

Ng T, Elkayam U et al :J CV Pharmacol Therap 2012;17:373

<table>
<thead>
<tr>
<th></th>
<th>Continuous infusion</th>
<th>Metolazone</th>
<th>Bumetanide</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hyponatremia</td>
<td>29%</td>
<td>43%</td>
<td>63%</td>
<td>0.011 **</td>
</tr>
<tr>
<td>Incidence of hypokalemia</td>
<td>27%</td>
<td>46%</td>
<td>29%</td>
<td>0.095</td>
</tr>
</tbody>
</table>
Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis 14000 AHF admissions


Metolazone use is independently associated with increased mortality. This survival disadvantage appears to be mediated predominantly by the hyponatremia and hypokalemia. Treatment of ADHF with high doses of loop diuretics demonstrated no survival disadvantage.
What is the dose?
intravenous acetazolamide (500 mg once daily) or placebo added to standardized IV loop diuretics (at a dose equivalent to twice the oral maintenance dose).

**Acetazolamide in acute heart failure with volume overload**

ADVOR Study


No difference in rate of hypokalemia
A title of a session in ACC 2023

Nephrology stopped the diuretics again ... Renal considerations in the management of heart failure.

How to deal with increased serum creatinine during diuresis?
Recommendations for diuretic Tx
ESC 2021, ACC/AHA/HFSA 2022

• Diuresis should not be discontinued prematurely because of small changes in serum creatinine.
• Elevations in the range of 0.3 mg/dL do not predict worse outcomes except when patients are discharged with persistent congestion.
• Increase Scr is not equivalent to WRF.
31% of 903 patients with ADHF developed ≥20% increased GFR (IRF). IRF was associated with greater incidence of post discharge WRF and increased mortality (HR 1.3, p=0.011)

Conclusions: IRF is associated with significantly worsened survival and may represent the resolution of venous congestion–induced preadmission WRF. Unlike WRF, the renal dysfunction in IRF patients occurs independently from the confounding effects of acute decongestion and may provide incremental information for the study of cardiorenal interactions. (J Cardiac Fail 2011;17:993–1000)

Key Words: Cardiorenal syndrome, worsening renal function, venous congestion.
Relevance of Changes in Scr During Heart Failure hospitalization
Insights From the DOSE Trial

• N=301 patients.
• Analysis of the effect of changes in Scr on 60 days mortality or rehospitalizations.
• WRF (Increased Scr > 0.3 mg/dL) was associated with lower risk (HR=0.81, P=.026)
• IRF (decreased Scr > 0.3 mg/dL) was associated with higher risk (HR 2.52, P<.001.

Brisco MA et al J Cardiac Fail 2016;22::753-60
WRF in Patients with AHF Undergoing aggressive Diuresis is not associated with Tubular Injury

• 283 patients in the ROSE-AHF trial.
• Mild to moderate increase in Scr occurred in 21%.
• There was no increase in the level of any of the markers of tubular injury.
• N-acetyl-beta-d-glucose aminidase (NAG)
• neutrophil gelatinase-associated lipocalin (NGAL)
• kidney injury molecule 1 were measured (KIM-1).

Improvement in Renal Function During the Treatment of Acute Decompensated Heart Failure: Relationship With Markers of Renal Tubular Injury and Prognostic Importance

Natov PS et al Circ Heart Fail. 2023;16:e009776.

Patients with IRF had lower GFR and higher Scr and BUN on admission.

IRF was not associated with improved markers of renal tubular injury and was associated with worsened survival, likely driven by the presence of greater underlying cardiorenal dysfunction and more severe congestion.
Is WRF an ominous prognostic sign in patients with ADHF?

Metra M et al Circ Heart Fail 2012; 5:54

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable HR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Cr Persistent congestion</td>
<td>2.44</td>
<td>0.0097</td>
</tr>
<tr>
<td>No change in Cr Persistent congestion</td>
<td>1.35</td>
<td>0.53</td>
</tr>
<tr>
<td>Increased Cr Congestion improved</td>
<td>1.04</td>
<td>0.88</td>
</tr>
<tr>
<td>No change in Cr Congestion improved</td>
<td></td>
<td>Reference</td>
</tr>
</tbody>
</table>

N=599
Relation Between Residual Congestion and Outcome
Prognostic value of residual pulmonary congestion at discharge by lung ultrasound imaging in heart failure

Coiro S et al Eu J Heart Fail 2015;17:1172-1181
What are the clinical implications?

• The goal of therapy is a relief of congestion.
• Diuretics resistance is common requiring high diuretic dosing.
• Addition of metolazone effective but associated with severe electrolyte abnormalities and increased mortality.
What are the clinical implications?

• Acetazolamide in addition to loop diuretics is effective and safe.

• Changes in Scr during the treatment of ADHF should be evaluated in the context of the overall clinical status.

• Increased Scr is associated with worse prognosis only in patients with persistent congestion.
Thank you

Uri Elkayam, MD
Professor of Medicine
University of Southern California School of Medicine
Los Angeles, California
elkayam@usc.edu